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The Patent Office

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1. Your reference

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2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SMITH & NEPHEW PLC
2 TEMPLE PLACE
VICTORIA EMBANKMENT
LONDON WC2R 3BP

Patents ADP number *(if you know it)*

03969284001

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

HYDROGEN BONDED COMPOUNDS

5. Name of your agent *(if you have one)*

J D HOBBS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

SMITH & NEPHEW GROUP RESEARCH CENTRE
GROUP PATENTS & TRADE MARKS DEPARTMENT
YORK SCIENCE PARK
HESLINGTON
YORK YO10 5DF
UNITED KINGDOM

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01166150 03

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Signature [signature] Date 26/07/99

J. D. HOBBS

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HYDROGEN BONDED COMPOUNDS

This invention relates to degradable polymer-like materials, in particular to such materials which are biodegradable, to precursors therefor and to artefacts made therefrom such as medical implant devices. More particularly the invention relates to polymer-like materials which can be formed into flexible constructs such as structural blocks, yarns and fibres.

In the conventional understanding of the term polymer, literally, many units, the component sub-units or precursors, eg. monomers or oligomers are bonded together *via* covalent linkages to form a high molecular weight material. Degradation of the polymer into lower molecular weight species occurs by scission of the covalent bonds binding the sub-units or by scission of a bond within one or more of the sub-units. For materials to biodegrade, the scission mechanism is usually a hydrolytic reaction. For a covalently bound polymer artefact to biodegrade completely, the hydrolysis of the polymer may take several years. Thus such polymers may have limited use in environments where constructs made from such polymers are required to have a temporary existence. Even in those cases where hydrolysis of the covalent bond, for example an anhydride linkage, takes place rapidly there has been no ability to control the precise nature of the degradation product. Thus, in some instances it may be desirable to degrade the polymer to lower molecular weight, non-toxic molecules, such as carbon dioxide and water, but in others it may be desired to form degradation products which are, themselves, beneficial, for example, exhibit a pharmaceutical effect.

Thus the present invention seeks to provide a class of materials which are capable of being formed into artefacts and yet

can be degraded in a predictable and controlled manner to form predictable fragments.

The materials of the present invention are characterised in that although they are polymer-like, the precursor residues are bonded to each other not by covalent bonds but by hydrogen bonds.

In accordance with the present invention there is provided a compound of the general formula (I):

(I)

where:

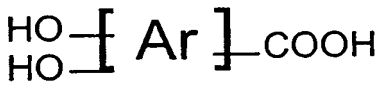
A may be the same or different and is a moiety containing at least four hydrogen bond donor and/or acceptor sites,

N may be the same or different and is a moiety containing at least one hydrogen bond donor and/or acceptor,

X may be the same or different and is a difunctional spacer linkage or unit and **n** is an integer having a value of at least one.

The moieties **A** and **N**, containing the donor and/or acceptance sites or groups, may be any of those known *per se*. Preferred moieties are those which contain hydroxyl and/or carboxyl groups.

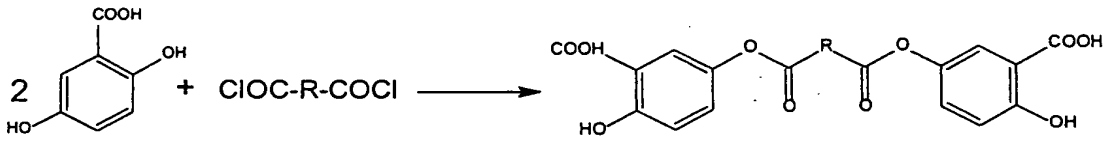
A is preferably an aromatic moiety, more preferably is an aromatic moiety of the general formula (II):



(II)

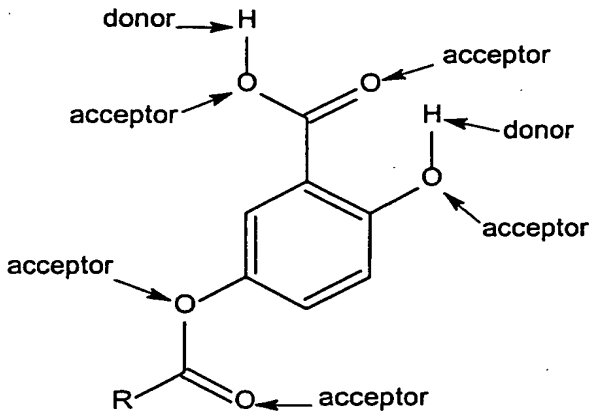
Where **Ar** is an unsubstituted or substituted aromatic nucleus e.g. phenyl or benzyl.

Preferred examples of compounds of Formula II are 2,5- and 2,3-dihydroxybenzoic acids: moieties capable of site-specific reactivity with the moiety **X**. For example, when **X** is an alkyl diacid chloride,



$R = (CH_2)_m$

The disposition of the terminal donor and acceptor sites in this compound may be represented thus



N is a moiety containing at least one hydrogen bond acceptance or donation site, aptly two or more hydrogen bond donation or acceptance sites, and may preferably contain at least three donors and/or acceptors. The moiety **N** may be the same or different as the moiety **A**. Aptly, where **A** and **N** are different, **A** may be 2,5-dihydroxybenzoic acid and **N** may be 3,5-dihydroxybenzoic acid.

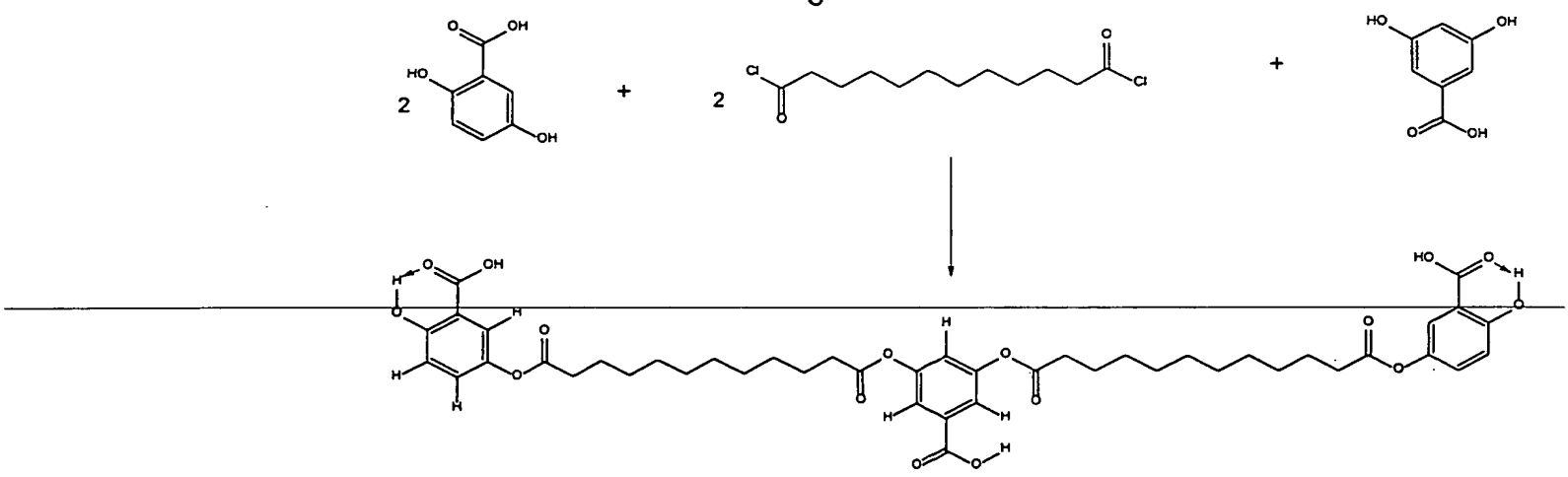
X is a difunctional linkage or residue and may be any moiety which does not have an adverse effect on the properties of the donor or acceptor groups. Suitably, **X** may comprise one or more groups which exhibit hydrophobic properties. Aptly, **X** will be a residue which will impart flexibility to aggregates, mixtures or polymers derived from compounds of the invention.

X is preferably comprised, in part or in total, of an alkylene group$(CH_2)_m$ where $m \geq 2$ and more preferably, an alkyl diacid, or functional derivative thereof, for example of the type,

$HOOC\text{-}(CH_2)_m\text{-}COOH$

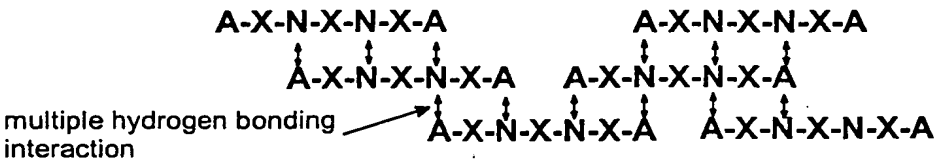
Aptly, the moiety **X** may be derived from long chain acid derivatives such as dodecandioyl dichloride, suberoyl chloride or sebacoyl chloride.

Reactants comprising the precursors of the moieties **A** and **N** and **X** are reacted to form covalent linkages between the species. The methods employed to carry out this reaction may by those conventionally employed. For example, **A** or **N** may be connected to **X** *via* an ester linkage by reacting **A** or **N**, comprising of at least one hydroxyl function, with an acid halide of **X** as shown by the following reaction scheme:



Compounds and mixtures, as defined above, and displaying aggregative properties in solution and/or in the molten state will henceforth be referred to as 'press-stud oligomers'. Aggregation of press-stud oligomers *via* the interaction of hydrogen bonding sites **A** and **N** allows the melt extrusion of fibres at elevated temperatures (>50 ^{0}C). Fibres so formed are self adherent and flexible immediately after extrusion. Aggregation can be probed by ^{13}C NMR spectroscopy and viscometric measurements against reference compounds lacking some/all hydrogen bonding functions.

The fibre forming properties of such aggregates, whilst not fully understood, are believed to be related to the abilility of the oligomers to align themselves under extrusion, as shown:



Press-stud oligomers are fibre-forming and may be composed of biocompatible and/or therapeutically active compounds (e.g. 2,5-dihydroxybenzoic acid) that are water soluble. Objects of the

present invention are press-stud oligomers, as defined above, the manufacture of these compounds and their applications as structural devices, drug delivery vehicles and adhesives, preferably medical devices.

Accordingly, the present invention further provides a composition of matter comprising an aggregate of at least one compound of Formula (I) herein.

Preferably such aggregates are water soluble.

The present invention also provides artefacts formed form the compositions of matter as described herein.

The invention will now be further descibed with reference to the following examples:

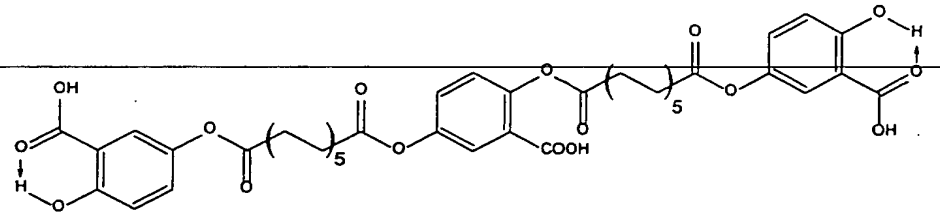
The composition or average structure of the materials exemplified below were confirmed by ^{1}H and ^{13}C NMR spectroscopy (d_8-THF, 270 MHz), Electrospray mass spectrometry and IR spectroscopy. The ^{1}H NMR spectroscopy characteristics for the materials produced are shown in the accompanying drawings in which

EXAMPLE	1	2	3	7
FIGURE	1	2	3	4

In all but example 3, the moieties **A** and **N** were the same: 2,5-dihydroxybenzoic acid (designated $\mathbf{G^{25}}$). In example 3, **A** was 2,5-dihydroxybenzoic acid ($\mathbf{G^{25}}$) and **N** was 3,5-dihydroxybenzoic acid ($\mathbf{G^{35}}$)

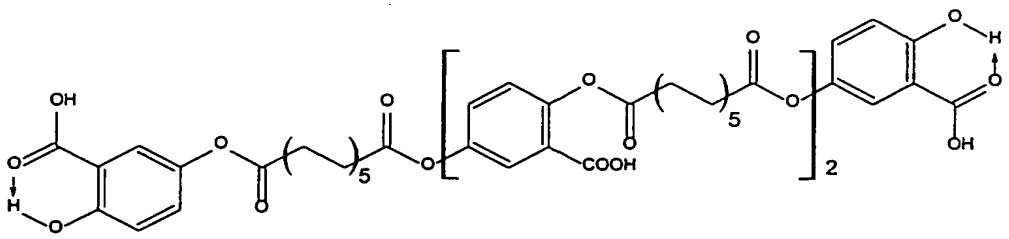
dihydroxybenzoic acid (G^{25}) and **N** was 3,5-dihydroxybenzoic acid (G^{35})

Example 1: Oligomers of the average structure ($G^{25}{}_3D_2$):



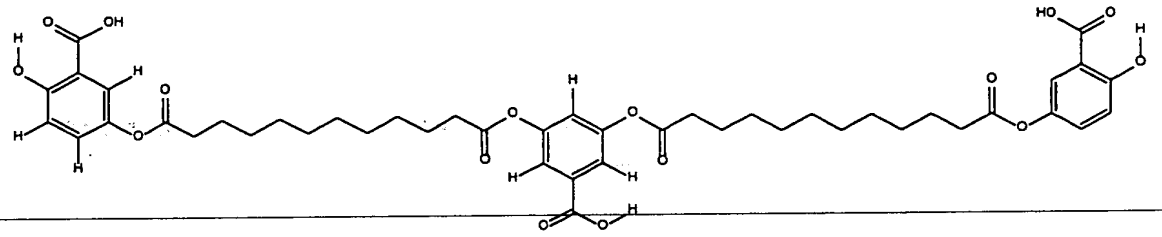
A magnetically stirred mixture of 4.435 g (29 mmol) of 2,5-dihydroxybenzoic acid and 5.126 g (19 mmol) of dodecanedioyl chloride (designated **D**) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

Example 2: Oligomers of the average structure ($G^{25}{}_4D_3$):



A magnetically stirred mixture of 2,5-dihydroxybenzoic acid (4.115 g, 27 mmol) and dodecanedioyl chloride (5.351 g, 20 mmol) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

Example 3: The discrete oligomer (G^{25}-D-G^{35}-D-G^{25}):



A magnetically stirred mixture of 3,5-dihydroxybenzoic acid (3.555 g, 23 mmol) and dodecanedioyl chloride (12.327 g, 46 mmol) was heated to 150 ^{0}C. The mixture was stirred until effervescence had subsided, after which 2,5-dihydroxybenzoic acid (7.110 g, 46 mmol) was added slowly. Following 10 minutes further heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

Example 4

$G^{25}{}_3Ad_3$ A magnetically stirred melt of 2,5-dihydroxybenzoic acid (5.097 g, 33 mmol) and adipoyl chloride (6.053 g, 33 mmol) (designated **Ad**) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

Example 5

$G^{25}{}_3Su_3$ A magnetically stirred melt of 2,5-dihydroxybenzoic acid (3.055 g, 20 mmol) and suberoyl chloride (4.184 g, 49 mmol) (designated **Su**) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

Example 6

$G^{25}{}_3Se_3$ A magnetically stirred melt of 2,5-dihydroxybenzoic acid (2.995 g, 19 mmol) and sebacoyl chloride (4.647 g, 19 mmol) (designated **Se**) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

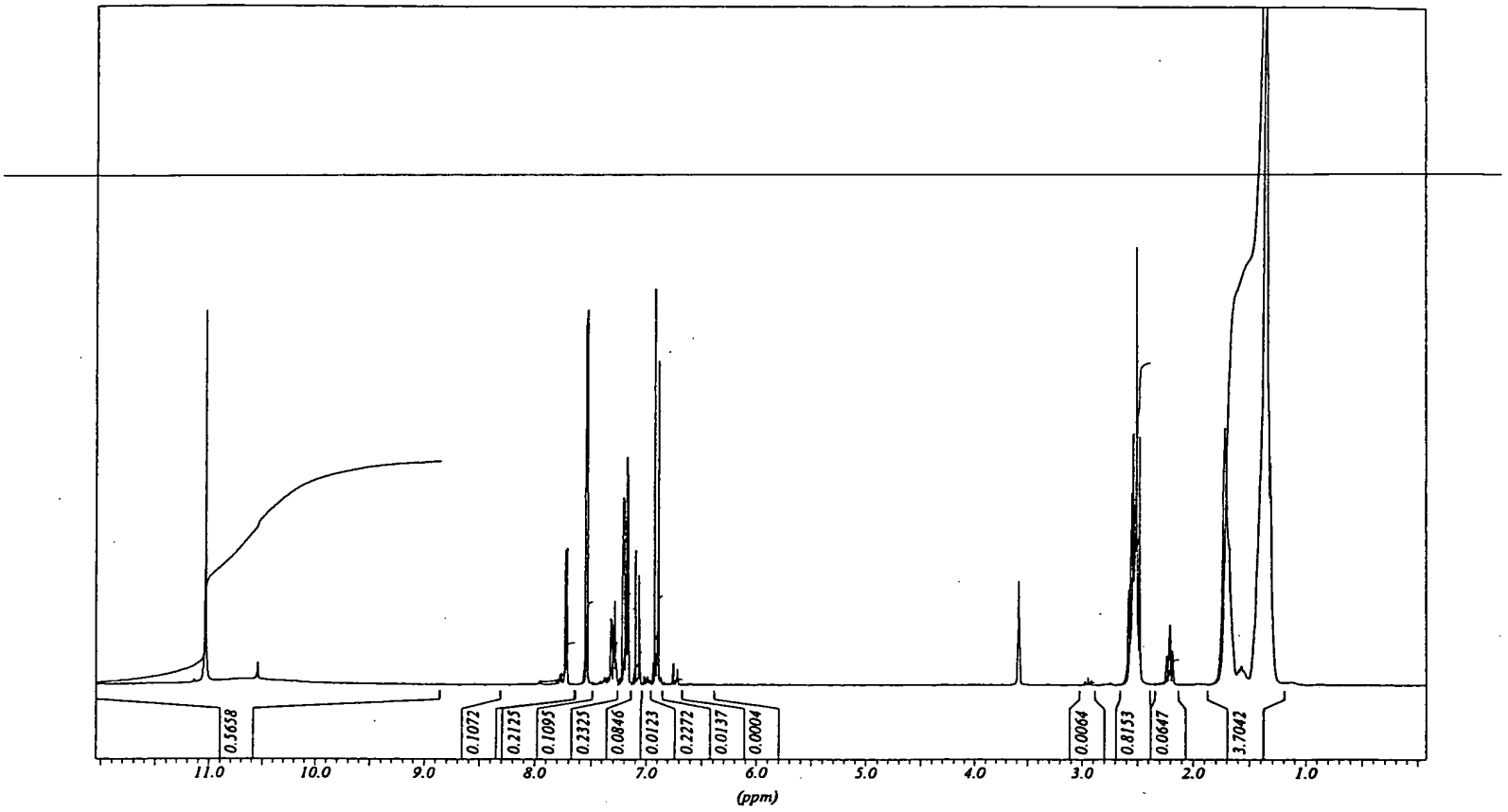
Example 7

$G^{25}{}_3D_3$ A magnetically stirred melt of 2,5-dihydroxybenzoic acid (7.518 g, 49 mmol) and dodecanedioyl chloride (13.034 g, 49 mmol) was heated to 150 ^{0}C. Following 10 minutes of heating at this temperature, the transparent viscous melt was cooled to room temperature and desiccated.

To confirm the hydrogen-bonded basis for the melt observations, methylated acid derivatives of **$G^{25}{}_3D_2$**, **$G^{25}{}_4D_3$**, and **$G^{25}{}_3D_3$** were prepared, respectively: **$MeG^{25}{}_3D_2$**, **$MeG^{25}{}_4D_3$**, and **$MeG^{25}{}_3D_3$**. The viscosities of these six compounds were measured, in duplicate, at 150 ^{0}C. The viscosity measurements are plotted in the graph shown Figure 5.

It can be seen that viscosities in the **G^{25}**-based compounds are greater, by an order of magnitude, than those measured for equivalent **MeG^{25}**-based compounds.

Fig.1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11.0
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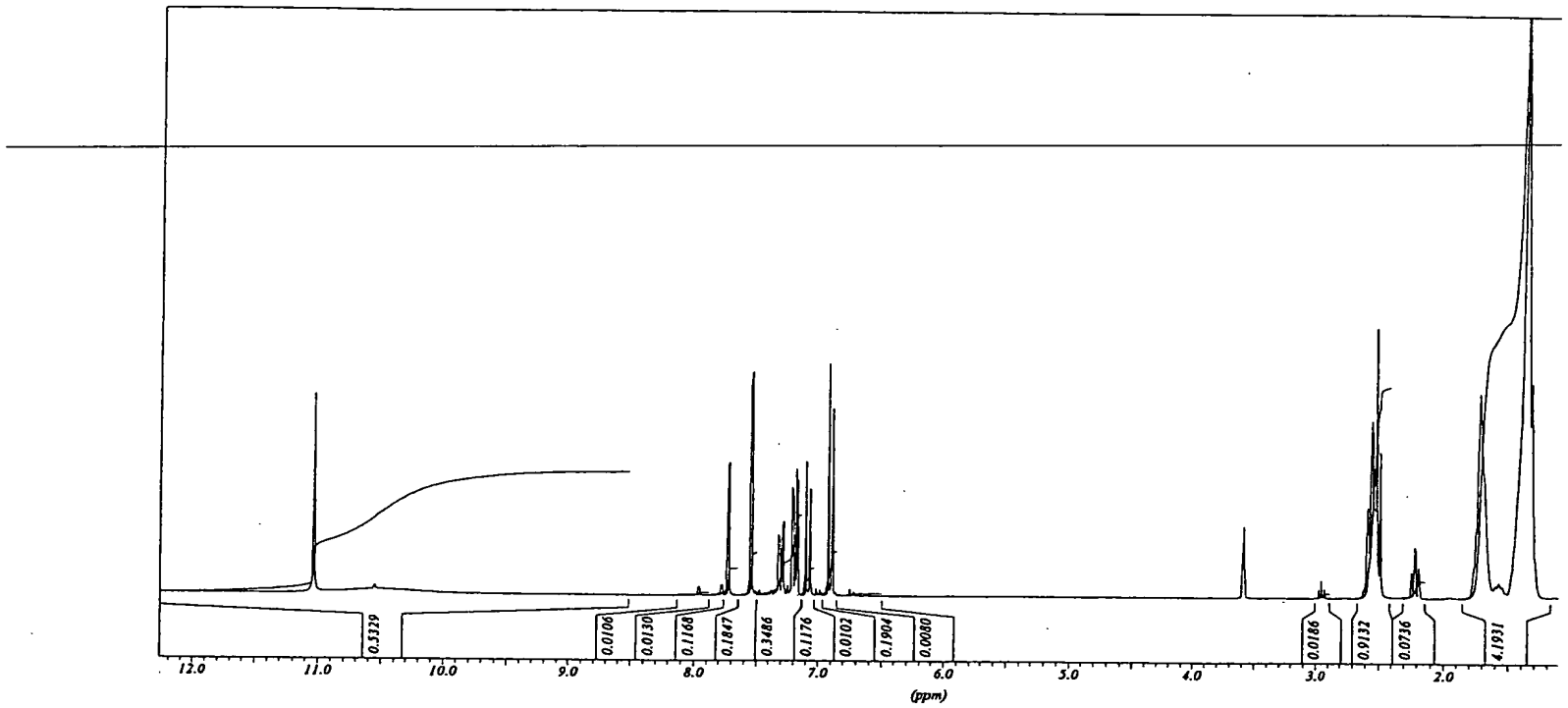
1.0
(ppm)

Fig. 2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2.0
(ppm)

Fig. 3

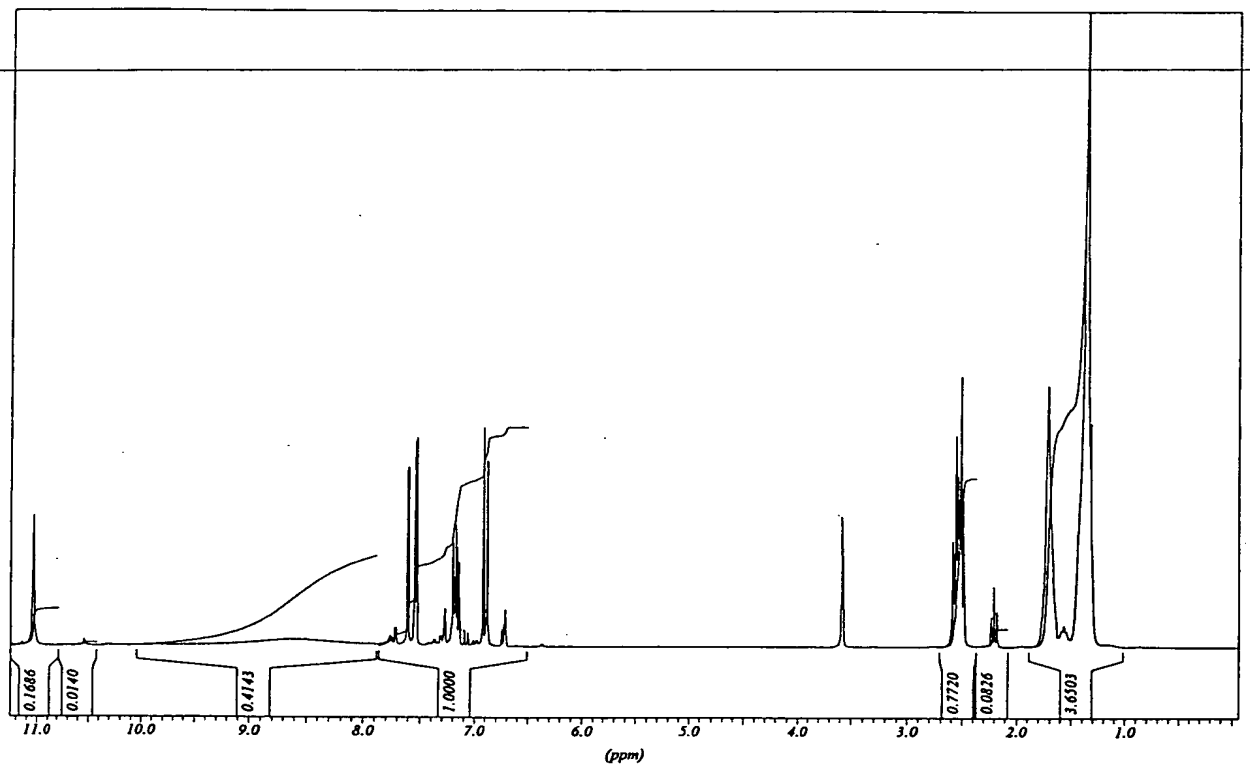
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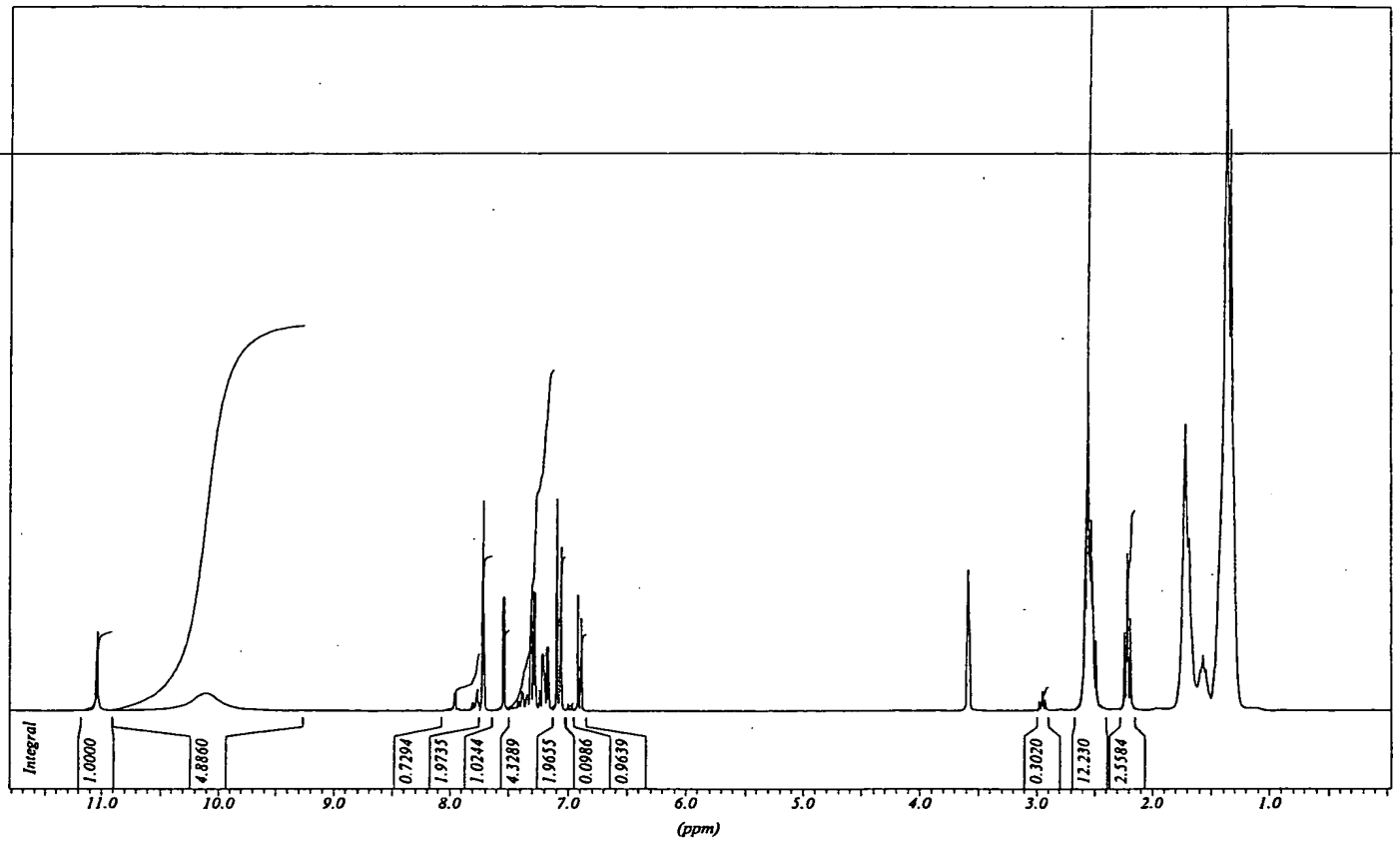
Fig. 4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12.230
2.5584
11.0
10.0
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7.0
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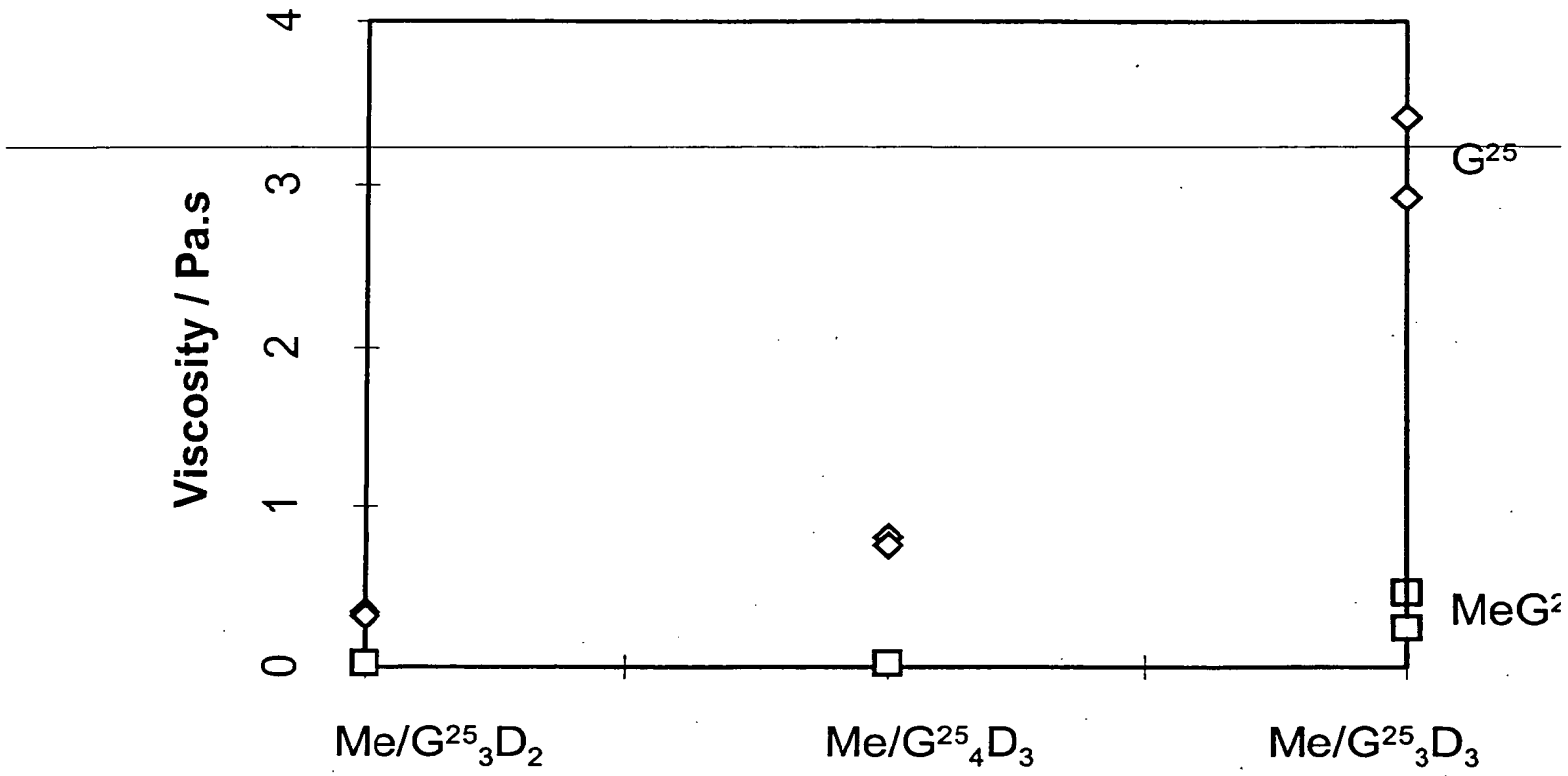
1.0
(ppm)

Fig. 5



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